Multidrug-Resistant Bacterial Colonization of Combat-Injured Personnel at Admission to Medical Centers After Evacuation From Afghanistan and Iraq

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Background: Multidrug-resistant organism (MDRO) infections, including those secondary to *Acinetobacter* (ACB) and extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (*Escherichia coli* and *Klebsiella* species) have complicated the care of combat-injured personnel during Operations Iraqi Freedom and Enduring Freedom. Data suggest that the source of these bacterial infections includes nosocomial transmission in both deployed hospitals and receiving military medical centers (MEDCENs). Admission screening for MDRO colonization has been established to monitor this problem and effectiveness of responses to it.

Methods: Admission colonization screening of injured personnel began in 2003 at the three US-based MEDCENs receiving the majority of combat-injured personnel. This was extended to Landstuhl Regional Medical Center (LRMC; Germany) in 2005. Focused on ACB initially, screening was expanded to include all MDROs in 2009 with a standardized screening strategy at LRMC and US-based MEDCENs for patients evacuated from the combat zone.

Results: Eighteen thousand five hundred sixty of 21,272 patients admitted to the 4 MEDCENs in calendar years 2005 to 2009 were screened for MDRO colonization. Average admission ACB colonization rates at the US-based MEDCENs declined during this 5-year period from 21% (2005) to 4% (2009); as did rates at LRMC (7–1%). In the first year of screening for all MDROs, 6% (171 of 2,989) of patients were found colonized at admission, only 29% (50) with ACB. Fifty-seven percent of patients (98) were colonized with ESBL-producing *E. coli* and 11% (18) with ESBL-producing *Klebsiella* species.

Conclusions: Although colonization with ACB declined during the past 5 years, there seems to be replacement of this pathogen with ESBL-producing Enterobacteriaceae.

Key Words: Infection control, Military, Trauma, *Acinetobacter*, *E. coli*, *Klebsiella*.

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Multidrug-resistant organism (MDRO; alternately, multidrug-resistant [MDR] bacteria) infections, including those secondary to *Acinetobacter baumannii-calcoaceticus* complex, extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (*Escherichia coli* and *Klebsiella* species), *Pseudomonas aeruginosa*, and methicillin-resistant *Staphylococcus aureus* (MRSA), have complicated the care of combat-injured US military personnel during Operations Iraqi Freedom and Enduring Freedom. Data suggest that the source of these infections includes nosocomial transmission in both deployed and fixed receiving medical treatment facilities (MTFs),[1–5] including from local national patients admitted to deployed MTFs.[6,7] Data for nosocomial dissemination of these MDROs are strongest for *Acinetobacter* (ACB).[1,4,8] Nosocomial spread of ACB from the combat zone has been reported from the United Kingdom and Canada as well.[9,10] The originating source of non-ACB MDR gram-negative bacteria and MRSA infections is less well understood. For MRSA, this source likely includes preexisting colonization of wounded personnel in addition to nosocomial transmission.[8,11] Measures to strengthen infection prevention and control (IC) efforts throughout the military healthcare system (MHS) have been implemented.[12–14] These include the production of clinical practice guidelines to prevent these infections and efforts to improve IC expertise and practice in the deployed setting. Clinical practice guidelines for the prevention of these infections from point of injury to definitive care in US tertiary care facilities were developed in 2007 and published in 2008.[14] IC expertise in the combat theater has been improved through increasing awareness of the problem, establishment of electronic resources to deployed healthcare providers, distribution of specific deployment IC standard

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operating procedure (SOP) templates, and the establishment of an IC short course for IC officers deploying to support hospitals in the combat theater.[12,13,15] To better track the scope of this problem and to monitor response to IC efforts, screening for MDRO colonization at admission to the military medical centers (MEDCENs) receiving the majority of US military casualties was established. Standardized screening at admission to these facilities should enhance the continued study of the source of MDRO infections in the combat-injured and provide more specific information to allow more directed IC interventions at probable source sites.

MATERIALS AND METHODS

Admission colonization screening began in 2003 at the three US-based military MEDCENs (Level V MTFs) that receive the majority of the US military combat-injured personnel: Brooke Army Medical Center (BAMC) in Fort Sam Houston, TX; National Naval Medical Center (NNMC) in Bethesda, MD; and Walter Reed Army Medical Center (WRAMC) in Washington, DC. This screening was extended in 2005 to those arriving directly from the combat zone to Landstuhl Regional Medical Center (LRMC; a Level IV MTF located in Germany). US military personnel evacuated from Iraq and Afghanistan underwent screening for colonization within 48 hours of admission to each of these four MEDCENs. LRMC received these personnel directly from the combat theater, whereas BAMC, NNMC, and WRAMC typically received these personnel from LRMC after they underwent initial stabilization, typically around 5 to 7 days after initial injury. Rarely, personnel were transported directly to one of the Level V facilities bypassing LRMC. Initially, this screening was limited to ACB (from 2003 to 2008) and was not standardized among these four facilities. Screening became fully standardized in 2008 and was expanded to include other MDROs in 2009. Data collected in 2003 and 2004 were not collected routinely within all care areas within the Level V facilities or from all admitted personnel. Therefore, only data from calendar years 2005 to 2009 are presented and discussed herein.

Admission Screening (2003–2008)

Screening for colonization at the four MEDCENs was based on local IC program SOP and not fully standardized across all four until the fall of 2008. Before 2009, admission screening was focused on detection of ACB, and this was the only bacteria reported within the group of MEDCENs for comparison. Body sites screened for colonization varied from facility to facility but included the groin at all MEDCENs. Other sites included at one or more facilities included nares, axillae, and the perirectal area. This screening was conducted with one or more commercially available culture swabs and standard clinical microbiology, including use of automated bacteriologic identification and susceptibility testing equipment (i.e., Phoenix Automated Microbiology System, BD; Franklin Lakes, NJ; and Vitek 2, bioMérieux, Inc., Durham, NC). Reporting also sometimes included data from detection of colonization from other clinically obtained cultures, including wounds. No universal or agreed upon definition of MDR ACB was in use during this screening period.

Standardized Screening (2009)

Infectious disease and infection prevention and control experts from the four participating MEDCENs, communicating through email and at specialty meetings, agreed to standardize admission screening and expand reporting from ACB to all MDRO bacteria. Work during the summer and fall of 2008 resulted in standardization of this screening and definitions of MDRO/MDR bacteria for this screening incorporated into each facility's IC program. Research conducted at WRAMC documented that the groin was the highest yield site to screen for ACB and other gram-negative MDR bacteria that colonize injured personnel.[3] Since the fall of 2008, admission screening has been conducted employing a single culturette to swab each patient's groin area bilaterally. This swab is plated on the standard bacteriologic media, and recovered bacteria are identified and susceptibilities performed using each hospital's clinical microbiology laboratory's automated system. Recovered bacteria were classified as MDRO/MDR based on the definitions agreed upon by the group (Table 1), these definitions closely mirror those in the current Centers for Disease Control and Prevention National Healthcare Safety Network manual.[16] Rates of MDRO admission colonization are reported by each facility monthly to the other participating facilities. Reporting includes number of patients admitted, number of patients screened, number of screened patients with MDRO colonization, and the specific MDR bacteria recovered. Rates tracked are simply the number of patients found to be colonized divided by the total number screened at each facility.

TABLE 1. Definitions Used to Identify MDRO/MDR Bacteria*

Gram-negative rods	
Any gram-negative rod that is resistant to all drugs tested in three or more of the following antimicrobial classes†	
Class	Antimicrobials
Aminoglycosides	Amikacin
	Gentamicin
	Tobramycin
β-lactams	Ampicillin/sulbactam
	Piperacillin/tazobactam
	Ceftazidime
	Cefepime
Carbapenems	Imipenem/cilastatin
	Meropenem
Fluoroquinolones	Ciprofloxacin
	Levofloxacin
Any gram-negative rod that produces extended-spectrum β-lactamase	
Stenotrophomonas spp., *Burkholderia cepacia*, and *Ralstonia* spp.	
Gram-positive cocci	
Methicillin-resistant *staphylococcus aureus*	
Vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*	

* Definition modified from reference 16.

† Resistance or susceptibility to other antimicrobials tested not belonging in one of the four listed classes (e.g., colistin, polymyxin, minocycline, tigecycline, and trimethoprim/sulfamethoxazole) should not be considered in the classification of isolates as MDRO/MDR bacteria.

Statistical Analysis

Data were analyzed with SPSS software program version 18 (SPSS for Windows; SPSS, Chicago, IL). To analyze the year-to-year differences in the mean proportions of positive screening isolates, a one-way analysis of variance was used. This test was also used to determine whether there were statistically significant differences in screening rates by month. Post hoc analysis was performed using Least Significant Difference and Bonferroni methods. Variables were tested for normality using the Kolmogorov-Smirnov test. To compare LRMC versus US-based admissions, a Mann-Whitney *U* test was used as assumptions of equality of variance and normality were not met. Evaluation of relationships between the absolute numbers and proportions of positive cultures against numbers of subjects admitted was performed with simple linear regression. A *p* value was considered statistically significant if $p < 0.05$. All confidence intervals are 95%.

RESULTS

Of 21,272 personnel admitted to the 4 MEDCENs in 2005 to 2009, 18,560 patients underwent screening for MDRO colonization at admission. Rates of ACB colonization at admission to the US-based Level V facilities (BAMC, NNMC, and WRAMC) declined during the 5-year period from 21% in 2005 to 4% in 2009 (Fig. 1 and Table 2). Rates at admission to LRMC similarly declined from 7% to 1% during this same time period.

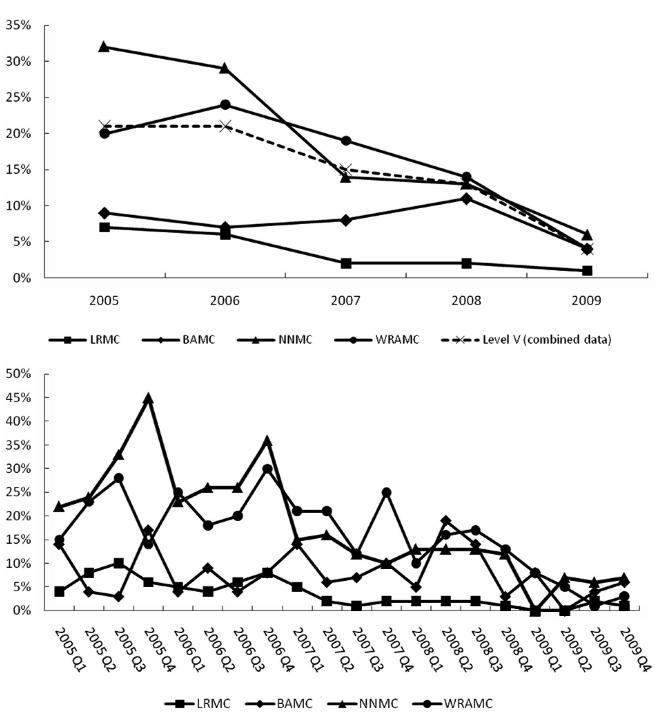

Figure 1. *Acinetobacter* colonization of US personnel evacuated from Operations Iraqi and Enduring Freedom at admission to receiving Level IV (LRMC), and Level V (BAMC, NNMC, and WRAMC) military medical centers, 2005–2009. Data displayed by year (top) and by quarter (bottom).

The mean proportion of patients with positive screening cultures decreased yearly in each hospital studied. These yearly changes were overall, significantly different from one another ($p < 0.01$); however, the proportions of positive cultures in 2005 and 2006 were equivalent, and those from 2007 and 2008 were also equivalent. The major, significant differences were seen in comparing these two time frames. Contrasting LRMC and US-based hospitals, LRMC had significantly lower proportions of positive screening cultures during all year's studies ($p < 0.01$). From 2005 until 2009, LRMC had 4% of their screening cultures positive, and US-based hospitals had 16% of their cultures positive. No single month had significantly higher rates of positive screening cultures than any other ($p = 0.6$). As the number of admissions increased, the absolute number of positive screening cultures increased ($r = 0.51$; $p < 0.01$). Interestingly, there was an inverse relationship between the percentage of positive cultures and numbers admitted ($r = -0.139$; $p = 0.032$). Although statistically significant, the relationship is weak and explains little of the variability seen in positive screening cultures from site to site and year to year ($r^2 = 0.116$).

In the first year of screening for all MDROs (2009), 171 of 2,989 patients (6%) were found to be colonized at admission, 3% of those admitted to LRMC, and 13% of those admitted to the Level V facilities (Table 3). Only 50 (29%) of those patients colonized with MDROs were found to have ACB colonization at screening. Ninety-eight patients (57%) were colonized with ESBL-producing *E. coli*, 18 (11%) with ESBL-producing *Klebsiella* species, 2 with MRSA, and 1 each with MDR *Pseudomonas*, *Citrobacter*, and *Enterobacter* species. Two patients had 2 MDRO recovered (i.e., a total of 173 isolates were recovered from 171 patients).

DISCUSSION

MDRO infections have become an international health problem during the past several decades and now pose a challenge to the care of our wounded military personnel. Although retrospective reviews of individual MEDCEN experiences have been published, comprehensive collection and interpretation of data regarding MDRO infection rates and patterns across the MHS in those US military personnel wounded in combat is not currently available.[4] Screening of personnel arriving from the combat theater at LRMC and being transferred from LRMC to the US-based MEDCENs can provide surrogate data on the effectiveness of IC measures in the combat zone and identify potential infectious disease (MDRO) threats to individuals and the MHS as a whole. Screening performed at these four MEDCENs reveals a decrease in the numbers of personnel arriving from the combat theater colonized with ACB and an associated decline during the reported 5-year period in those arriving at the US-based centers colonized. However, it is not clear why the rates of colonization are much higher at admission to the Level V facilities. Potential explanations include contamination at LRMC from other colonized patients or healthcare personnel or expansion of low-level colonization to detectable colonization secondary to time and exposure to broad-

TABLE 2. *Acinetobacter* Colonization of US Personnel Evacuated From Operations Iraqi and Enduring Freedom at Admission to Receiving Level IV (LRMC) and Level V (BAMC, NNMC, and WRAMC) Military Medical Centers, 2005–2009

	LRMC	BAMC	NNMC	WRAMC	Combined Level V*	Total
2005						
Personnel screened	2,743	261	276	609	1,146	3,889
Personnel ACB positive	187	24	89	124	237	424
ACB colonization rate (95% CI)	7% (5.8–7.8)	9% (5.7–12.7)	32% (26.7–37.8)	20% (17.6–23.6)	21% (18.3–23.0)	11% (9.92–11.9)
2006						
Personnel screened	2,728	268	350	532	1,150	3,878
Personnel ACB positive	159	18	100	127	245	404
ACB colonization rate (95% CI)	6% (5.0–6.7)	7% (3.7–9.7)	29% (23.8–33.3)	24% (20.3–27.5)	21% (18.9–23.7)	10% (9.5–11.4)
2007						
Personnel screened	3,530	366	261	559	1,186	4,716
Personnel ACB positive	81	31	37	109	177	258
ACB colonization rate (95% CI)	2% (1.2–2.3)	8% (5.6–11.3)	14% (10.0–18.4)	19% (16.2–22.8)	15% (12.9–17.0)	5% (4.8–6.1)
2008						
Personnel screened	2,254	222	140	472	834	3,088
Personnel ACB positive	40	25	18	66	109	149
ACB colonization rate (95% CI)	2% (1.2–2.3)	11% (7.1–15.5)	13% (7.3–18.4)	14% (10.9–17.1)	13% (10.8–15.4)	5% (4.1–5.6)
2009						
Personnel screened	2,256	169	193	371	733	2,989
Personnel ACB positive	18	7	11	14	32	50
ACB colonization rate (95% CI)	1% (0.5–1.2)	4% (1.1–7.1)	6% (2.4–9.0)	4% (1.8–5.7)	4% (2.9–5.9)	2% (1.2–2.1)

* Combined data from the three participating Level V facilities—BAMC, NNMC, and WRAMC.
CI, confidence interval.

TABLE 3. MDRO Colonization of US Personnel Evacuated From Operations Iraqi and Enduring Freedom at Admission to Receiving Level IV (LRMC) and Level V (BAMC, NNMC, and WRAMC) Military Medical Centers, 2009

	LRMC	BAMC	NNMC	WRAMC	Combined Level V*	Total
Personnel screened	2,256	169	193	371	733	2,989
Personnel MDRO positive	78†	27	23	43	93	171†
MDRO colonization rate (95% CI)	3% (2.7–4.2)	16% (10.5–21.5)	12% (7.4–16.5)	12% (8.3–14.9)	13% (10.3–15.1)	6% (4.9–6.6)
Acinetobacter species	18	7	11	14	32	50
Escherichia coli (ESBL)	52	11	10	25	46	98
Klebsiella species (ESBL)	7	8	0	3	11	18
MRSA	1	1	2	0	3	4
Enterobacter cloacae	0	0	0	1	1	1
Pseudomonas aeruginosa	1	0	0	0	0	1
Citrobacter species	1	0	0	0	0	1

* Combined data from the three participating Level V facilities—BAMC, NNMC, and WRAMC.
† Two LRMC patients were colonized with two MDROs, one with *Acinetobacter* species/ESBL *E. coli* and one with ESBL *Klebsiella* species/*Citrobacter* species.
CI, confidence interval.

spectrum antibiotics.[8,17,18] Our results also support a shift in the MDRO threat from ACB to ESBL-producing *E. coli* and *Klebsiella* species. This is supportive of what has been reported anecdotally in the military infectious disease community during the past 1 to 2 years and is supported by studies from within the combat theater.[6,7] As screening for non-ACB MDROs was not uniformly performed until 2009, it is not clear whether these have suddenly appeared in the system or whether they have only recently expanded to detectable levels, although these organisms have been reported from both BAMC and WRAMC during the past few years.[3,4,19]

Since the first recognition of higher than expected rates of ACB infection in 2003,[20,21] much work has been done to better understand the source of these infections and to ameliorate or prevent their spread. Investigations to date suggest that, at least for ACB, these MDR bacteria are chiefly being spread by nosocomial transmission[1,2] and not through preexisting colonization[22,23] or inoculation at the time of injury.[11] In response to this problem, clinical practice guidelines have been produced, and clinical microbiology equipment and personnel have been deployed to the combat theater to improve patient care and to help to limit the use of overly

broad-spectrum antibiotics.[14,24] Two missions have been conducted specifically to review the infection control challenges and practice at hospitals in the combat zone.[12,13] These missions have resulted in recommendations to medical leadership to enhance IC expertise on-the-ground in the combat theater, to better emphasize basic IC measures, to further standardize IC and use of established guidelines, and to limit the overuse of antimicrobial agents. As a direct result of these missions, an IC short course has been established to help train IC officers who are deploying to combat theater hospitals,[15] and IC electronic resources to support deployed healthcare personnel have been developed.[12] These include establishment of a telemedicine consultation service and web-based access to published guidelines, which is continuously updated. A theater-wide IC SOP template has been developed and adopted. Of great importance, results and trends of the admission screening data reported here has been fed back in real-time to medical leaders in the combat theater to allow reevaluation of IC practice and to investigate possible MDRO outbreaks.

More recently, several major long-term efforts have been established to better track and evaluate the MDRO problem. These include one large scale prospective research study and the establishment of performance improvement-based bacterial repository with associated surveillance network and an infectious disease module to supplement the current Joint Theater Trauma Registry. The "Trauma infectious diseases outcomes study" or TIDOS is a joint Department of Defense/Department of Veterans Affairs study administered by the Infectious Disease Clinical Research Program to study the risk factors, interventions, and outcomes associated with MDRO infections in the combat injured. The Multidrug-Resistant Organism Repository and Surveillance Network is a performance improvement-based organization, which has been established to advise military medical leaders about MDRO epidemiology. The Joint Theater Trauma Registry infectious disease module has been developed to allow data collection that should provide better clarity on the use of antimicrobial therapy and bacteria that complicate specific wounds and wounding patterns.

Limitations of the current study include the lack of understanding as to whether a direct association exists between MDRO colonization and eventual infection. Although we have further delineated the MDRO colonization trends in personnel evacuated from the combat zone, the true risk of infection associated with this colonization needs to be further examined. Even if a direct association can be established, it is also unclear whether attempts to decolonize patients can effectively prevent later infection. Data have been presented that chlorhexidine baths can decrease ACB colonization and subsequent bacteremia,[25] and this has not been proven in the combat trauma population. The Joint Theater Trauma System clinical practice guidelines currently include the suggestion to bath intensive care patients in the combat theater daily with chlorhexidine-containing cloths.

Implementation and emphasis of IC measures seem to have impacted the rate of colonization with ACB in this population. It is less clear whether noted colonization with other MDRO represents increasing, decreasing, or stable rates among non-ACB bacteria, but clearly ESBL *E. coli* is emerging as a MDRO of increasing importance. Awareness of the colonization pattern of the combat wounded can be used to improve care by allowing better selection of empirical antibiotics, targeted IC efforts, and feedback to the originating site of patient evacuation. Currently, admission screening for MDRO colonization provides the best near real-time data to track and attempt to prevent MDRO infections in our combat-injured personnel.

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